Advanced systemic mastocytosis: an uncommon cause of chronic diarrhea and weight loss

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We report a case of 64-year old man with symptoms of diarrhea, fatigue, weight loss and progressive abdominal swelling with hepatomegaly since four months, eventually presenting with an upper gastro-intestinal bleeding with multiple duodenal ulcers. Blood analysis showed a grade 1 anemia and thrombocytopenia, a pronounced monocytosis, and cholestatic liver function tests. Further diagnostic work-up revealed hepatosplenomegaly with signs of portal hypertension, a vertebral compression fracture and multiple 18-FDG avid supra- and infradiaphragmatic lymph nodes and bone marrow. The diagnosis of a systemic mastocytosis (SM) was made based on strongly elevated serum tryptase levels, multifocal nests of CD25 positive mast cells with a spindle shaped appearance infiltrating the bone marrow, a lymph node, the pancreas and liver, and the presence of the KIT c.2447A>T (p.D816V) mutation in the bone marrow; thereby fulfilling the major and all of the four minor criteria of the 2016 WHO criteria of SM (1)(2)(3). Given the presence of >= 1 C-findings, the diagnosis of aggressive systemic mastocytosis (ASM) was made (4)(5); based on the concomitant CMML, the diagnosis of ASM with an associated hematological neoplasm (AHN) was reached. The patient started on midostaurin, a tyrosine kinase inhibitor (TKI) active against p.D816V mutated *KIT* (6), achieving clinical response, as defined by the IWG-MRT & ECNM (7), after six months of treatment. Subsequently, six cycles of cladribine were administered, inducing a partial response (decrease of serum tryptase levels >50%, > 50% reduction of spleen size and bone marrow mast cell infiltration) (7). Because of persistent disease, avapritinib was initiated, a novel tyrosine kinase inhibitor recently approved by FDA for PDGFRA exon 18 (including D842V) mutant GIST, with promising activity against *KIT* c.2447A>T (p.D816V) mutated ASM (8). Avapritinib led to normalisation of serum tryptase levels, and undetectable levels of the *KIT* c.2447A>T (p.D816V) mutation (detection threshold 0,006%), despite persisting monocytosis. Because of hematological toxicity and neurological side effects, avapritinib had to be interrupted. Currently, the patient is still in follow-up.

The diagnosis of advanced systemic mastocytosis can be challenging due to its diverse signs and symptoms, eventually all attributable to mast cell infiltration and mediator release, in this case well illustrated by diarrhea, multiple duodenal ulcers, osteoporosis with vertebral compression fractures, cytopenias, hepatomegaly with portal hypertension, hypersplenism and malabsorption. The advent of a novel TKI with activity against p.D816V mutated *KIT* can induce biochemical and molecular remission in ASM. The resistance of the AHN CMML remains ununderstood.

References:

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 19;127(20):2391–405.

2. Valent P, Horny H-P, Li CY, et al. Mastocytosis (mast cell disease). In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues. France: IARC Press Lyon; 2001:291-302. In.

3. Horny HP, Akin C, Metcalfe DD, et al. Mastocytosis (mast cell disease). In: Swerdlow SH, Campo E, Harris NL, et al, eds. World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008:54-63. In.

4. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res. 2001 Jul;25(7):603–25.

5. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017 16;129(11):1420–7.

6. Chandesris M-O, Damaj G, Canioni D, Brouzes C, Lhermitte L, Hanssens K, et al. Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016 Jun 30;374(26):2605–7.

7. Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013 Mar 28;121(13):2393–401.

8. Deininger MW, Gotlib J, Robinson WA, et al. Avapritinib (BLU-285), a selective KIT inhibitor, is associated with high response rate and tolerable safety profile in advanced systemic mastocytosis: results from a phase 1 study. EHA Annual Meeting, 2018.